Determinants of the Timing of Symptomatic Treatment in Early Parkinson Disease

The National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD) Experience

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Objective: To assess the predictive value of baseline measures of impairment, disability, and quality of life for the timing of initiation of symptomatic treatment in early Parkinson disease (PD).

Design: Inception cohort analysis.

Setting: Ambulatory population from multiple sites in the United States and Canada.

Participants: Four hundred thirteen patients with early, untreated PD who participated in 2 double-blind trials that assessed the potential of experimental drugs to serve as disease-modifying agents in PD.

Intervention: Participants were randomized into treatment groups: creatine (n = 67), minocycline (n = 66), coenzyme Q10 (n = 71), GPI-1485 (n = 71), and placebo (n = 138).

Main Outcome Measure: Time between baseline assessment and need for the initiation of symptomatic treatment for PD. The following baseline variables were assessed for their relation to the main outcome measure, while adjusting for possible treatment effect: sex; age; level of education; race/ethnicity; disease duration; occupational status; and Unified Parkinson Disease Rating Scale (UPDRS), Medical Outcomes Study Short Form Survey, Modified Rankin Scale, Schwab and England Activities of Daily Living Scale, Total Functional Capacity Scale, 39-item Parkinson Disease Questionnaire, and Geriatric Depression Scale scores. Variables reaching statistical threshold in univariate analyses (α = .15) were entered into a multivariable Cox proportional hazards regression model using time to symptomatic treatment as the dependent variable.

Results: Approximately half (48.5%) of the participants reached end point within 12 months. Higher baseline impairment and disability, as determined by UPDRS III (motor section), UPDRS II (activities of daily living section, participant rating), and Modified Rankin Scale scores and level of education were independently associated with an earlier need for symptomatic treatment.

Conclusions: In early PD, greater impairment and disability and higher level of education are independently associated with an earlier need for symptomatic treatment.

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Parkinson disease (PD) is a chronic progressive neurodegenerative disease that leads to significant morbidity, disability, and increased likelihood of institutionalization.1,2 In view of the potential for short-term and long-term drug complications, symptomatic treatment is customarily delayed in PD until the severity of motor symptoms results in functional impairment.3 Therefore, the initiation of symptomatic treatment is considered an early indicator of disease progression in PD and is used as an important benchmark in clinical trials.4-7 As part of the National Institutes of Health Exploratory Trials in Parkinson Disease (NET-PD), 2 futility drug studies explored the potential of 4 compounds to serve as disease-modifying agents in early, untreated PD. The primary outcome measure of these studies was change in the total Unified Parkinson Disease Rating Scale (UPDRS) score from baseline to the time at which there was sufficient disability to warrant symptomatic treatment. Participants in these 2 studies were assessed with a number of impairment, disability, and quality of life measures at baseline visit. The usefulness of such measures in the earliest stages of PD is not well under-
stood, and their relationship to functional impairment is unknown. In the present exploratory analysis, we examined the relative value of these baseline measures as predictors of the time of symptomatic treatment initiation. We hypothesized that quality of life and emotional factors as well as factors measuring physical disability would be associated with time to initiation of symptomatic therapy.

METHODS

PARTICIPANTS

Data from the 413 participants in the 2 NET-PD futility trials (Futility Study 1 [FS-1] and Futility Study 2 [FS-TOO]) were used for this analysis. Both trials were multicenter, randomized, double-blind studies designed to assess the futility of candidate drugs as disease-modifying agents in outpatients with early, untreated PD. Participants were men and women aged 30 years and older with a diagnosis of PD for 5 years or less, who did not require any medications for the treatment of their PD symptoms at the time of study entry. Two of 3 cardinal manifestations of PD (tremor, rigidity, and bradykinesia) were required for the diagnosis; these signs had to be asymmetric. Other potential causes of parkinsonism or prior brain surgery for PD were exclusion criteria. Women of childbearing potential had a negative pregnancy test result at baseline and were required to use adequate birth control for the duration of the study. All participants gave written informed consent. The protocols and consents for the drug trials were approved by a National Institute of Neurological Disorders and Stroke oversight board, an independent data safety monitoring board, and the institutional review boards of the participating sites.

BASELINE ASSESSMENTS

At the baseline visit, demographic data were collected, including sex, age, level of education, race/ethnicity, disease duration (from diagnosis), and (for FS-TOO participants only) occupational status. The UPDRS III (motor section) was administered as a measure of impairment. The following scales were administered to measure disability: UPDRS II (activities of daily living [ADL] section; completed by both the investigator and the participant)10; Modified Rankin Scale11; Schwab and England ADL Scale (completed by both the investigator and the participant)12; Total Functional Capacity Scale13; and the ADL subscale of the 39-item Parkinson Disease Questionnaire (PDQ-39).14 The PDQ-39 (all subscales and the summary index) and the Medical Outcomes Study Short Form Survey (SF-12)15 were administered as indicators of quality of life. The UPDRS I (mentation, behavior, and mood section), completed both by the investigator and participant, and the Geriatric Depression Scale16 were also administered to provide information on mental and cognitive functions at baseline. In calculating the total UPDRS score, only sections completed by the investigator were used.

TREATMENTS

In each of the futility studies, participants were randomized in a 1:1:1 ratio to receive 1 of the 2 active experimental drug treatment arms or placebo. Of the 200 FS-1 participants, 67 received creatine, 66 minocycline, and 67 placebo, while 71 of 213 FS-TOO participants received coenzyme Q10, 71 GPI-1485, and 71 placebo.

END POINT DETERMINATION

The primary end point for the analyses in this study was time to initiation of symptomatic treatment. Symptomatic treatments included levodopa, dopamine agonists, amantadine, anticholinergics, and selegiline. Cases were censored at 12 months of follow-up if they had not reached the end point by that time. Site investigators used their clinical judgment to determine when participants had reached a level of dysfunction sufficient to require symptomatic therapy in any of 3 areas: ambulation, activities of daily living, or occupational status.5,8,9

STATISTICAL ANALYSIS

Baseline variables were screened to assess their relationship with time to the initiation of symptomatic therapy using Cox proportional hazard regression. Regression models adjusting for experimental drug group assignment were used to test the association of each independent variable separately with the primary end point according to the Hosmer and Lemeshow model of development strategy17; any baseline variable associated with the initiation of symptomatic therapy at an α level of .15 was selected for inclusion in multivariable model construction. We adjusted for experimental drug group assignment, because we hypothesized that the drugs studied could potentially impact time to symptomatic treatment. Spearman rank correlations among all pairwise combinations of selected variables were also calculated to assess potential collinearity prior to proceeding with the multivariable model development.

A multivariable Cox proportional hazard regression model with time to initiation of symptomatic treatment as the dependent variable was constructed using the selected variables and experimental drug group. Restricted backwards selection was used to remove baseline variables meeting the exclusion criteria of a greater than .05 while forcing the experimental drug group assignments to remain in the model, as we did not assume absence of an experimental drug effect. Proportional hazard assumptions were checked after each step and at the derivation of the final model. The Harrell concordance index18 was also estimated after the final model as a measure of agreement between the model’s prediction and the observed events: a concordance of 0.5 indicates no agreement between prediction and observation and 1.0 indicates perfect agreement.

The analysis was completed using SAS, version 9.2 (SAS Institute Inc, Cary, North Carolina), and Stata, version 9.2 (Stata Corp, College Station, Texas).

RESULTS

BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Table 1 summarizes the baseline demographics of the patient population along with baseline impairment, disability, and quality of life measures. Two hundred of a total sample of 413 participants (48.5%) started symptomatic treatment within 12 months of baseline.

Demographics, Impairment, Disability, and Time to End Point

In the exploratory screening phase of the analyses, greater baseline impairment and disability, lower quality of life, and higher education level were associated with earlier need for symptomatic treatment (Table 1). More specifically, the following variables met criteria and were selected for inclusion in the multivariable model: level of education; sex; and UPDRS I, UPDRS II, UPDRS II (par-
Strong correlations were identified between total UPDRS and UPDRS II and III scores, with Spearman correlation coefficients of 0.75 for section II and 0.92 for section III. The correlation coefficient between the PDQ-39 Mobility Subscale and the PDQ-39 summary index was 0.70. Pairwise correlations between the subscale scores were weak; therefore, the UPDRS section scores and PDQ-39 subscale scores were retained, while the total UPDRS score and PDQ-39 summary index were excluded from subsequent consideration in the multivariable model. Despite a strong correlation between the investigator- and participant-reported UPDRS II scores (correlation coefficient, 0.80), both variables were retained in the multivariable model, as the data were derived from different sources (investigator vs participant).

The final model, based on completion of the restricted backward selection of variables, adjusted for experimental drug assignment and included education and UPDRS III, UPDRS II (participant report), and Modified Rankin Scale scores (Table 2). Eight participants (1.9%) were excluded from this analysis owing to incomplete data. This model was confirmed to produce the largest overall Pearson \( \chi^2 \) statistic of other competing models. The Harrell concordance index was 0.665. Proportional hazard assumptions were satisfied at every backward step and the final model. Kaplan-Meier curves of the final 4 covariates are shown in the Figure.

### Table 1. Baseline Variables Classified by End Point

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Symptomatic Therapy(^a) (n=213)</th>
<th>Symptomatic Therapy Initiated(^b) (n=200)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y(^c)</td>
<td>62.0 (10.7)</td>
<td>61.3 (10.1)</td>
<td>.77</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.8 (3.3)</td>
<td>15.7 (3.0)</td>
<td>.01 (^d)</td>
</tr>
<tr>
<td>Time from PD diagnosis, y</td>
<td>0.7 (0.9)</td>
<td>0.6 (0.8)</td>
<td>.77</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>60.1</td>
<td>68.5</td>
<td>.12 (^d)</td>
</tr>
<tr>
<td>White race, %</td>
<td>88.3</td>
<td>94.0</td>
<td>.36</td>
</tr>
<tr>
<td>Working full-time, %(^e)</td>
<td>42.6</td>
<td>43.4</td>
<td>.52</td>
</tr>
</tbody>
</table>

**Scale score**
- UPDRS III | 14.3 (6.3) | 17.6 (6.8) | <.001 \(^d\) |
- UPDRS I | 1.0 (1.4) | 1.2 (1.3) | .09 \(^d\) |
- UPDRS II | 5.1 (2.9) | 6.9 (3.3) | <.001 \(^d\) |
- UPDRS, total | 20.4 (8.5) | 25.8 (9.1) | <.001 \(^d\) |
- UPDRS I, participant reported | 1.7 (1.7) | 1.6 (1.5) | .97 |
- UPDRS II, participant reported | 5.8 (3.4) | 7.5 (3.8) | <.001 \(^d\) |
- SF-12, Physical Summary | 50.7 (7.4) | 49.3 (7.8) | .01 \(^c\) |
- SF-12, Mental Summary | 51.6 (9.4) | 51.2 (8.7) | .66 |
- Participants with Modified Rankin Scale scores >1, % | 6.6 | 17.0 | <.001 \(^d\) |
- Schwab and England ADL Scale | 94.1 (5.3) | 91.9 (5.1) | <.001 \(^d\) |
- Schwab and England ADL Scale, participant reported | 94.1 (6.5) | 91.9 (6.4) | <.001 \(^d\) |
| TFC | 12.5 (0.9) | 12.2 (1.5) | .01 \(^d\) |
| PDQ-39, Mobility | 8.1 (12.8) | 12.2 (13.9) | <.001 \(^d\) |
| PDQ-39, ADL | 13.1 (14.0) | 19.0 (15.9) | <.001 \(^d\) |
| PDQ-39, Emotional | 19.1 (18.7) | 20.3 (17.5) | .21 |
| PDQ-39, Stigma | 14.1 (18.9) | 17.4 (18.3) | .01 \(^d\) |
| PDQ-39, Social | 8.3 (16.6) | 5.6 (11.8) | .35 |
| PDQ-39, Cognition | 17.0 (17.9) | 17.1 (16.5) | .93 |
| PDQ-39, Communication | 12.3 (18.5) | 14.9 (18.5) | .08 \(^d\) |
| PDQ-39, Discomfort | 26.9 (22.1) | 28.4 (20.5) | .65 |
| PDQ-39, summary index | 14.8 (12.2) | 16.8 (11.1) | .01 \(^d\) |
| GDS | 2.0 (2.4) | 2.3 (2.7) | .11 \(^d\) |

**Abbreviations:** ADL, activities of daily living; GDS, Geriatric Depression Scale; PD, Parkinson disease; PDQ-39, 39-item Parkinson Disease Questionnaire; SF-12, Medical Outcomes Study Short Form Survey; TFC, Total Functional Capacity Scale; UPDRS, Unified Parkinson Disease Rating Scale.

\(^a\) End point not reached.

\(^b\) End point reached.

\(^c\) Ages older than 89 years were collapsed to 90 years.

\(^d\) Variable reaching threshold for inclusion in the multivariable analyses.

\(^e\) Measured only in Futility Study 2 (N=200).

In the 2 NET-PD futility trials, a greater degree of impairment and disability at baseline was associated with...
The disease characteristics of PD among the NET-PD futility trial participants were similar to those of participants in previous studies of putative disease-modifying agents, and they were typical of early PD.5,6,19

Although only 3 of the impairment and disability measures used in the NET-PD futility trials showed strong, independent correlations with time to end point in a multivariable model, all such measures obtained at baseline as well as the quality of life measures used (ie, total UPDRS, Modified Rankin Scale, Schwab and England ADL Scale, Total Functional Capacity Scale, SF-12 Physical Summary Subscale, and PDQ-39 summary index) tracked well with time to end point in the exploratory univariate analyses. Scores on subscales related to motor functioning, such as UPDRS III, UPDRS II (participant report), SF-12 Physical Summary Subscale, PDQ-39 Mobility Subscale, and PDQ-39 ADL Subscale, showed significant associations with time to end point. However, subscales associated with cognitive, psychiatric, and social functioning, including UPDRS I, UPDRS I (participant report), SF-12 Mental Summary Subscale, and the Emotional, Social, Cognitive, Communications, and Discomfort Subscales of the PDQ-39 were not associated with the end point, with the exception of the PDQ-39 Stigma Subscale. This dichotomy suggests that motor dysfunction is the most prominent baseline determinant of how soon the need for symptomatic treatment may arise.

Similar to the 2 NET-PD futility studies, data from the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) Study59 have been analyzed using time to symptomatic treatment as a primary end point.20 Analyses of baseline variables among participants in DATATOP have also identified greater disability (UPDRS II score, Schwab and England ADL Scale score, and self-reported difficulty with ADL and domestic capacity) and worse motor function (total, motor, and tremor, rigidity, postural stability, and bradykinesia scores on the UPDRS, perceived threat to gait and balance; Purdue Pegboard Test result; and Hoehn and Yahr stage) as significant predictors of earlier need for symptomatic treatment in early PD.20 Contrary to DATATOP, we found no association between participant-reported UPDRS I scores and only a statistically nonsignificant trend between higher investigator UPDRS I scores and shorter time to end point. This apparent discrepancy may be a consequence of the different statistical treatment of this variable (it was treated as dichotomous in the DATATOP analyses), or it might reflect the somewhat less advanced disease state among the NET-PD futility trial participants than in the DATATOP participants.8,9,19

While both impairment and disability assessments were predictive of the timing of symptomatic treatment, we found no significant correlations between UPDRS III (the impairment measure used in this analysis) and the disability measures. It is likely that this paradox arises from the relative insensitivity of disability measures in early PD. To illustrate the point, only 11% of our sample population had a Modified Rankin Scale score greater than 1, and the median Schwab and England ADL Scale score was 95%. This resulted in heavily skewed distributions of the disability ratings, which failed to attain robust correlations with the more evenly distributed impairment measure (UPDRS III).

The only PDQ-39 subscale that correlated highly with the PDQ-39 summary index was the Mobility Subscale, suggesting that mobility is the most important determinant of quality of life in patients with early PD as measured by this scale. The quality of life measures related to mobility, ADL, and stigma showed associations with time to end point, while the emotional, social, cognitive, communications, and discomfort subscales did not. Stigma has been reported as an important determinant of quality of life, particularly among patients with younger-onset PD.21 In the multivariable model, motor impairment and disability were retained, while stigma and depression were not. This suggests that stigma is more likely related to motor impairment, rather than independent emotional or psychiatric factors.

The relatively lesser role of emotional factors at baseline in determining the need for symptomatic treatment is supported by the absence of a significant association between baseline Geriatric Depression Scale score and time to symptomatic treatment. However, a recent analysis of the same data set22 found that a higher degree of depression (when Geriatric Depression Scale score was treated as a time-dependent variable) was a significant predictor of earlier symptomatic treatment. The prior analysis assessed the impact of increasing depression, rather than the severity of depression at baseline, on the same outcome. Taken together, the results of these 2 analyses suggest that the severity of depression at baseline has no impact on the timing of the need for symptomatic treatment; however, a subsequent increase in depressive symptoms is associated with earlier need for symptomatic treatment. Given the lack of association between baseline Geriatric Depression Scale scores and time to symptomatic treatment in the present analysis and the strong association between Geriatric Depression Scale score and UPDRS II score progression found in the previous analysis,21 an alternative interpretation is that both the increasing severity of depression and an earlier de-

Table 2. Final Cox Regression Model (n=405)2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education, 4-year increment</td>
<td>1.38 (1.16-1.65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>UPDRS III, 1-point increment</td>
<td>1.04 (1.01-1.06)</td>
<td>.001</td>
</tr>
<tr>
<td>UPDRS II, participant reported, 1-point increment</td>
<td>1.08 (1.04-1.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Modified Rankin Scale, &gt;1 vs ≤1</td>
<td>1.73 (1.15-2.61)</td>
<td>.009</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; UPDRS, Unified Parkinson Disease Rating Scale.

a Adjusted for experimental drug assignment, P = .78.
cision to initiate symptomatic treatment are the parallel consequences of increasing disability, rather than increasing depression solely driving the decision to initiate symptomatic treatment. An interesting observation stemming from the comparison of the 2 analyses is that while some measures may be more informative at baseline, others may be more useful in monitoring disease activity during follow-up.

The level of education was the only demographic feature that was associated with time to initiation of symptomatic treatment, with higher education correlating with earlier symptomatic treatment. Such an association was not evident in the earlier analysis of the DATATOP data set. This discrepancy may be due to the variable being statistically treated as dichotomous in the earlier study. A possible explanation is that higher education may be associated with greater occupational demands and an increased need for symptomatic control. However, one might expect that occupations placing higher demands on physical abilities (usually associated with lower education levels) would be associated with a more pressing need for symptomatic control. An alternate possibility is that patients with higher education are likely to be better advocates for their health care needs and play a more active role in medical decision-making. The results of this study are consistent with the association between higher education and increased use of health care services previously found in PD and indicate that education level has a complex relationship with PD outcomes.

Although we found no association between disease duration at baseline and time to symptomatic treatment ini-
tiation, time from symptom onset longer than 2 years was reported as a significant predictor of earlier treatment in the DATATOP study. The variable used in our study is not directly comparable with that from the DATATOP study, as we analyzed duration from disease diagnosis. Sex and employment status were not statistically significant in either study.

In conclusion, in this early stage of the disease, baseline measures associated with earlier introduction of symptomatic impairment included UPDRS III (motor), UPDRS II (ADL, participant rating), and Modified Rankin Scale scores and education. Emotional, psychiatric, and quality of life factors at baseline played a smaller role in determining need for symptomatic treatment and did not enter the final model when baseline impairment, disability, and education were taken into account. The impact of the patient’s education level on clinical management is an unexpected finding and merits further investigation.

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Author Contributions: All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Parashos, Swearingen, Biglan, Bodis-Wollner, Liang, Ross, Tilley, and Shulman. Acquisition of data: Parashos, Biglan, Bodis-Wollner, Liang, Ross, and Shulman. Analysis and interpretation of data: Parashos, Swearingen, Biglan, Bodis-Wollner, Liang, Ross, Tilley, and Shulman. Drafting of the manuscript: Parashos, Swearingen, Tilley, and Shulman. Critical revision of the manuscript for important intellectual content: Parashos, Swearingen, Biglan, Bodis-Wollner, Liang, Ross, Tilley, and Shulman. Administrative, technical, and material support: Parashos, Swearingen, Tilley, and Shulman. Study supervision: Shulman.

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